
Human Embryonic Stem Cells Do Not Change Their X Inactivation Status during Differentiation.

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Public Summary:

Applications of embryonic stem cells (ESCs) require faithful chromatin changes during differentiation, but the fate of the X chromosome state in differentiating ESCs is unclear. Female human ESC lines either carry two active X chromosomes (XaXa), an Xa and inactive X chromosome with or without XIST RNA coating (XiXIST+Xa;XiXa), or an Xa and an eroded Xi (XeXa) where the Xi no longer expresses XIST RNA and has partially reactivated. Here, we established XiXa, XeXa, and XaXa ESC lines and followed their X chromosome state during differentiation. Surprisingly, we found that the X state pre-existing in primed ESCs is maintained in differentiated cells. Consequently, differentiated XeXa and XaXa cells lacked XIST, did not induce X inactivation, and displayed higher X-linked gene expression than XiXa cells. These results demonstrate that X chromosome dosage compensation is not required for ESC differentiation. Our data imply that XiXIST+Xa ESCs are most suited for downstream applications and show that all other X states are abnormal byproducts of our ESC derivation and propagation method.

Scientific Abstract:

Applications of embryonic stem cells (ESCs) require faithful chromatin changes during differentiation, but the fate of the X chromosome state in differentiating ESCs is unclear. Female human ESC lines either carry two active X chromosomes (XaXa), an Xa and inactive X chromosome with or without XIST RNA coating (XiXIST+Xa;XiXa), or an Xa and an eroded Xi (XeXa) where the Xi no longer expresses XIST RNA and has partially reactivated. Here, we established XiXa, XeXa, and XaXa ESC lines and followed their X chromosome state during differentiation. Surprisingly, we found that the X state pre-existing in primed ESCs is maintained in differentiated cells. Consequently, differentiated XeXa and XaXa cells lacked XIST, did not induce X inactivation, and displayed higher X-linked gene expression than XiXa cells. These results demonstrate that X chromosome dosage compensation is not required for ESC differentiation. Our data imply that XiXIST+Xa ESCs are most suited for downstream applications and show that all other X states are abnormal byproducts of our ESC derivation and propagation method.

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